(IA2). Insulin was also mentioned as an ICA (see page 1 of Exhibit 3). This date of 22 August 1996 predates both the Borg et al. and the Wiest-Ladenburger et al. references which have been relied upon for the rejection. Both of those references are from 1997. Borg et al. was cited for its teaching that antibodies to GAD and IA2 are useful in the diagnosis of diabetes. The Declaration and Exhibits show that Applicant was in possession of this knowledge prior to the publication of the Borg et al. reference. The Wiest-Ladenburger et al. reference was cited for its teaching that in most individuals developing IDDM, ICAs are markers for the disease and that IA2 and GAD65 represent a major subfraction of ICAs. Again, the Declaration and Exhibits show that Applicant was in possession of this knowledge prior to the publication of the Wiest-Ladenburger et al. reference. In view of the Declaration and Exhibits showing conception of the invention prior to the publication dates of the two cited papers, it is urged that the Borg et al. and the Wiest-Ladenburger et al. references cannot be cited against the present invention. Because these two references were relied upon to make the rejection, it is urged that the rejection must fail and it is requested that the rejection be withdrawn.

Claims 1-10 and 17-18 were rejected under 35 U.S.C. 103(a) as obvious over Rogers et al., in view of Hummel et al., Verge et al., Rabin et al., Borg et al., Berg et al., and Wiest-Ladenburger et al. and further in view of WO 94/07464. The only difference between this rejection and that described above is the inclusion of WO 94/07464 as a teaching of biotin or streptavidin as part of the fusion protein which is a limitation of claim 6. As discussed just above, the rejection relies upon the Borg et al. and the Wiest-Ladenburger et al. references which, in view of the attached Declaration and Exhibits, cannot be cited against the claims of the present application. In view of this it is requested that the rejection be withdrawn.

Claims 19-20 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Rogers et al. in view of Hummel et al., Verge eta l., Rabin et al., Borg et al., Berg et al., and Wiest-Ladenburger et al. and further in view of WO 94/07464 and Xu et al. or Hemmila et al. Again, the rejection relies upon the Borg et al. and the Wiest-Ladenburger et al. references. The attached Declaration and references show conception of the invention prior to the publication of these two references. It is requested that this rejection be withdrawn.

In addition to overcoming two of the cited references which were relied upon, Applicant reiterates that the rejection should also fail for the reasons set forth in the Amendment filed on 16 December 1999. One point from the Remarks of the Amendment of 16 December 1999 will be further commented on. It was urged that the claimed fusion proteins would form a three dimensional structure with exposed epitopes not predictable from the cited prior art and therefore it would have been unpredictable whether any appropriate epitopes would be accessible to the antibodies to be used. The Office Action of 28 February 2000 responded to this argument by stating that there was no evidence of record to indicate the state of the art at the time the invention was made teaches that making fusion proteins comprising more than one epitope is unpredictable. That statement does not respond to the argument set forth in the Amendment. It was not urged that fusion proteins containing more than one epitope could not be made, rather it was urged that when several peptide fragments are linearly linked to form a large protein it was unpredictable at the time of the invention as to how such a synthetic protein would fold and whether it would fold in a manner which resulted in the known epitopes being exposed and available to react with antibodies. The three dimensional structures of such synthesized proteins was not known and was not predictable and it was not known what epitopes would be exposed. Submitted herewith are searches made of MedLine and of the Protein Data Bank. These searches were performed on May 17, 2000. None of the searches resulted in a finding of a reference which teaches the folding of GAD65 or ICA 512 (IA2). Because the folding of these proteins is not presently known, it is urged that the folding of these proteins at the time of the invention was also unknown and that the folding of a fusion protein comprising these proteins was unknown and unpredictable at the time of the invention. Because of the differences between the claims and the cited prior art, i.e., the fact that such recombitopes had never been made, that the claimed recombitopes can be very large, and that specific protein fragments were not clearly known to include appropriate epitopes, the prior art at best leads to an obvious to try analysis.

In view of the arguments set forth above and in the Amendment submitted 16 December 1999, it is requested that the rejections of the claims under 35 U.S.C. § 103(a) be withdrawn.

In view of the amendments and the above arguments, it is submitted that the present claims satisfy the provisions of the patent statutes and are patentable over the prior art. Reconsideration of this application and early notice of allowance are requested.

Respectfully submitted,

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